2.0 SCIENTIFIC ABSTRACT

Approximately 47,000 cases of cutaneous melanoma were diagnosed in the U.S. in 2000. About two-thirds of patients present with limited (Stage I or II) disease and most of these can be surgically cured. Patients with Stage III disease have regional nodal metastases and can occasionally be cured by surgical resection. The remainder, however, ultimately die from recurrent or progressive disease. There are no curative or standard treatment approaches for patients with Stage III disease who relapse or for patients who present with distant metastases (Stage IV).

High-dose bolus administration of IL-2 protein leads to responses in 17% of metastatic melanoma patients, including 7% complete responders, a few of which are durable. IL-2 administration, however, is associated with significant adverse effects, including capillary leak, pulmonary edema, fever, hypotension and renal and cardiac adverse effects.

Other cytokines with potential anti-tumor benefits include IFN-a and IL- 12. Plasmid-based transfer of the genes encoding these cytokines offers the possibility of concentrated, local expression to obtain beneficial anti-tumor effects without the toxicities often associated with the systemic administration of recombinant cytokines.

A clinical trial has been designed which aims to evaluate the safety and tolerability of direct intratumoral injection of a combination of human IL-12- and IFN-a-encoding plasmid-based therapeutics in patients with unresectable cancer. In the dose escalation phase of the trial, up to five cohorts of three to six patients with accessible metastatic cancers will receive four doses of formulated plasmid over four weeks. Safety and tolerability will be assessed and the maximum tolerated dose determined. In the efficacy portion of the trial, from 10 to 25 additional patients with metastatic melanoma will be treated with eight doses over seven weeks at the maximum tolerated dose. The portion of patients with complete or partial response will be assessed with the aim of determining whether the intervention is likely to have a true response rate of at least 10%.